REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons commentary.

Cancellation is requested for claims 3-10, 13, 18-20 and 24-27. Applicants seek revision of claims 1, 11, 14, 16 and 21-23. Thus, the present response revises or deletes claims in this application. Accordingly, applicants present a detailed listing, with an appropriate status identifier, of each claim that is or was in the application, irrespective of whether the claim remains under examination..

With entry of the changes set forth above, claims 1, 2, 11, 12, 14-17, 21-23, 28 and 29 are will be pending.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 10-12, 14, 15, 26, 28 stand rejected as being anticipated by Rosner, *Acta Neurologica Latinoamerican*a, Vol. 21(1-4), 1975, pp. 126-132.

The foregoing changes obviate the stated basis for this rejection. Amended claim 1 recites "arsenic trioxide." Since Rosner fails to teach the use of arsenic trioxide, it cannot anticipate the claims. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 2, 16-17 and 21-25 stand rejected over Rosner in view of Repetto *et al.*, CN 1121807, CN 1121807, CN 1079391 and JP 51-88620. Applicants respectfully traverse this rejection on the basis that a *prima facie* case of obviousness has not been established.

A *prima facie* case must satisfy three criteria. First, the cited prior art must teach or suggest each of the claim limitations. *In re Royka,* 490 F.2d 981, 985 (CCPA 1974). Second, the cited reference(s) must provide some suggestion or evidence some motivation, in light of the knowledge attributable to the person of ordinary skill, to modify the prior art to arrive at the

claimed invention. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Third, the prior art must evidence that persons of ordinary skill in the art would have had a reasonable expectation of success in achieving the invention, via the modification or combination posited by the examiner. *Id.* "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not the applicant's disclosure" (*Id.*) in order to avoid the "insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *In re Kotzab,* 217 F.3d 1365, 1369 (Fed. Cir. 2000). For the reasons discussed below, these criteria have not been met.

Applicants assert that the cited art fails to establish a *prima facie* case of obviousness. Nevertheless, without prejudice and to further the prosecution of the application, Applicants have amended all claims to further specify that the arsenic compound in all claims is arsenic trioxide.

The Office Action cites Rosner as disclosing the treatment of brain cancer and intracranial neoplasm in humans with mapharsen and carbarsone (Office Action, page 3, last paragraph). Both mapharsen and carbarsone are organic arsenic compounds. The evidence and arguments of record fail to show how Rosner's disclosure would have led a skilled artisan to substitute the organic arsenic compounds with inorganic arsenic compounds, particularly arsenic trioxide, or expect that such inorganic arsenic compounds would be efficacious in treating the solid tumors as presently claimed.

Rather than overcoming the deficiencies of Rosner, Repetto *et al.* would have led a person skilled in the art away from the claimed invention. Repetto *et al.* describe an *in vitro* neuropathy model for evaluating the cytotoxic effects of sodium arsenite and sodium arsenate, representing the trivalent and pentavalent states of arsenic, respectively. The authors are able to evaluate the environmental effect of arsenic exposure. Neuroblastoma cells are used as an immortalized cell line model to determine the likelihood of physical damage to an animal's nervous system by arsenic exposure. The study is not a disease treatment study and one must be very careful in applying it to that context.

Moreover, in disease treatment neuropathy is not a desirable effect. In fact, neuropathy is a detrimental side effect of disease treatment and is a factor in the suitability of treatment at all. In this way, if it can be applied to disease treatment, the Reppeto *et al.* study would have to be viewed from the context of the suitability of arsenic compounds to treat disease at all, not as a measure of its effectiveness.

The authors conclude that As (III) is five times more toxic to neural cells than As (V). Thus, if applied to disease treatment, the results of Repetto *et al.* would have led a skilled artisan to conclude that arsenicals, particularly those with a +3 oxidation state, would likely exert undue harmful effects on the nervous system when used as a therapeutic treatment. Since arsenic trioxide includes arsenic in the +3 oxidation state, Repetto *et al.*'s toxicology study, if applied to disease treatment, discounts the value of arsenic trioxide as too toxic as a therapeutic.

JP 51-88620 also fails to overcome the deficiencies of Rosner as it similarly fails to disclose arsenic trioxide.

While CN 1079391 describes arsenic preparations for treating skin cancer and cervical cancer, it acknowledges that such traditional Chinese preparations "are still unable to touch upon in vivo cancer tumors." English translation of CN 1079391, at page 7, first paragraph. Moreover, CN 1079391 provides no scientific basis or experimental results supporting the use of arsenic compounds, particularly arsenic trioxide, in the treatment of other types of cancer, including solid tumors as presently claimed.

CN 1121807 relates to the use of arsenic trioxide to treat acute promyelocytic leukemia (APL). Yet positive results in treating APL would not have led the skilled artisan to predict similar results when treating other cancers, including solid tumors as presently claimed.

For example, APL stands alone amongst the various cancers in having a 17:15 chromosomal translocation, which is a primary cytogenic feature characteristic of this subtype of acute myeloid leukemia. For this reason, APL can be treated with all-trans retinoic acid (ATRA).

When arsenic trioxide was found to be effective in treating APL, those of skill in the art looked for a mechanism similar to that found for ATRA. In particular, Chen *et al.*, *Blood*, 89:3345-3353 (1997), copy attached, disclose that APL is associated with the t(15:17) translocation, which generates a PML/RAR fusion protein between PML, a growth suppressor localized on nuclear matrix-associated bodies and RAR, a nuclear receptor for retinoic acid (RA). Based on their results, Chen *et al.* conclude that in APL cells, arsenic trioxide degrades PML/RAR proteins, and induces NB_4 cell apoptosis with down-regulation of Bcl-2 expression and modulation of PML proteins. Thus, the art identifies a particular mechanism, ***specific to APL and APL cells***, by which arsenic exerts its effects. In light of this specific mode of action, the evidence and arguments of record fail to prove that a skilled artisan would have expected arsenic compounds to be effective in treating other types of cancer, including solid tumors as presently claimed.

In contrast to APL, solid tumors are not associated with the t(15;17) defect. Nothing in the cited references suggests that arsenic trioxide might have a mechanism of action that would lend itself to treating solid tumors. Rather, the art teaches that arsenites are highly toxic compounds. Thus, Office fails to establish a *prima facie* case of obviousness with respect to the use of arsenic trioxide for treating solid tumors.

Based on the foregoing reasons, applicants respectfully request withdrawal of this rejection.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 30 June 2004

By _____

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.